RICC Updates

RePORT Meetings 2017
Rio de Janeiro, Brazil

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Professor of Medicine, Duke University
Outline/topics

- Scientific Progress
- Operational Progress
- Common Protocol
- Data standardization, issues
- Biological Specimens: Numbers, future sharing
- RePORT-wide Projects
- Future
Scientific progress

• Each consortium has been funded at different times
• Parent protocol versus Common Protocol
• Funding timelines for RePORT Common Protocol:

- Brazil 2013
- South Africa 2015
- India 2015/16
- Indonesia 2016
- China 2017
## RePORT Consortium Site Status for Common Protocol enrollments (as of August 2017)

<table>
<thead>
<tr>
<th>Country</th>
<th>Cohort A (Active TB)</th>
<th>Cohort B (HHC)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># sites enrolling</td>
<td># sites expected to enroll</td>
</tr>
<tr>
<td>India</td>
<td>3</td>
<td>5</td>
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<tr>
<td>Brazil</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>South Africa</td>
<td>5</td>
<td>7</td>
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<tr>
<td>Indonesia</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>China</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>33</td>
</tr>
</tbody>
</table>
## RePORT Consortium Site Status for Common Protocol enrollments (as of August 2017)

<table>
<thead>
<tr>
<th>Country</th>
<th>Cohort A (Active TB)</th>
<th>Cohort B (HHC)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># enrolled</td>
<td># expected</td>
</tr>
<tr>
<td>India</td>
<td>51</td>
<td>1700</td>
</tr>
<tr>
<td>Brazil</td>
<td>522</td>
<td>900</td>
</tr>
<tr>
<td>South Africa</td>
<td>309</td>
<td>1115</td>
</tr>
<tr>
<td>Indonesia</td>
<td>78</td>
<td>1357</td>
</tr>
<tr>
<td>China</td>
<td>2</td>
<td>160</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>962</td>
<td>5232</td>
</tr>
</tbody>
</table>
ENROLLMENTS OVER TIME: COHORT A

Cohort A

- 2015: 0
- 2016: 200
- 2017: 1000
18 peer-reviewed publications resulting from RePORT activities (majority from India site, parent protocol work), but also including two describing the vision and goals for RePORT International.
Publications & Presentations

• Symposium accepted, planned for International Union meetings, October 12

02. Regional Prospective Observational Research in TB (RePORT) International: biomarkers of TB and comorbidities across Brazil, India and South Africa

RePORT International builds upon collaborations between US investigators and those based in high-burden settings with co-funding from local governments and the US National Institutes of Health’s (NIH) National Institute of Allergy and Infectious Diseases (NIAID) and Division of AIDS (DAIDS).

Objectives for participants include:
1. Understanding the goals and methods the RePORT network utilizes to facilitate data and specimen sharing.
2. Learning how immunologic signatures are informing new biomarkers of TB progression and severity, including in TB-diabetes and TB-HIV co-infection.
3. Increasing knowledge about how the investigations are shaping new diagnostic options for children.

The topics are of relevance to researchers and government policy makers to consider for the direction of future programmatically relevant research.

Carol Hamilton
Roanna Rustomjee

<table>
<thead>
<tr>
<th>Introduction of RePORT International</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudha Srinivasan, United States of America</td>
</tr>
<tr>
<td>A brief summary of RePORT International vision, country members and goals will be presented</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Approaching TB diagnostics using transcriptional and cytokine signatures in TB-HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valeria Rollo, Brazil</td>
</tr>
</tbody>
</table>

V Rollo

1National Institute of Infectious Diseases Evandro Chagas - Fiocruz, LAPCLIN-TB, Rio de Janeiro, RJ, Brazil; Fax: +552138659607. e-mail: valeria.rollo@gmail.com

There have been advances in the diagnosis of patients with TB based on nucleic acid amplification of bacteria in sputum. However, HIV-infected individuals often remain undetected even in the setting of more advanced diagnostics such as GenXpert MTB/RIF where sensitivity is < 70%. A number of promising new host biomarkers of TB infection, disease and treatment response now have the potential to impact the diagnosis of TB in HIV-infected individuals.
Outline/topics

• Scientific Progress: consortia site status, enrollments, samples, publications/presentations, new projects

• Operational Progress: Website, Bylaws, SAB, Executive Committee (EC) calls
  – Comments, utility, communication?

• Common Protocol: updates, changes
  – Issues?

• Data: Recognized problems from RICC
  – Discuss solutions

• Specimens: tracking, future sharing, begin decision making discussions
OPERATIONAL PROGRESS

• Bylaws: Approved by EC, posted on website
  – Established Steering Committee comprising 1 PI from each site
    • Pending: Have not elected Chair of the Steering committee
  – Have not yet constituted standing committees except EC: Science Committee; Publications & presentations committee
    • Is it time?
OPERATIONAL PROGRESS

- Bylaws: Approved by EC, posted on website
- Executive committee calls
  - Frequency, work, comments?
- Website
  - https://www.reportinternational.org/
Website Launched in July

- Central place to get current versions of protocols, manuals, CRFs
- Public face of RePORT International
- Living document: check for news; inputs and suggestions welcome
OPERATIONAL PROGRESS

• Bylaws: Approved by EC, posted on website
• Executive committee calls
  – Frequency, work, comments?
• Website
  – https://www.reportinternational.org/
• Scientific Advisory Board (SAB)
Welcome Gavin and Susan!
OPERATIONAL PROGRESS

• Executive committee calls
  – Frequency, work, comments?

• Website
  – https://www.reportinternational.org/

• Scientific Advisory Boards (SAB)

• Comments, discussion, suggestions?
Outline/topics

• Scientific Progress: consortia site status, enrollments, samples, publications/presentations, new projects
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Common Protocol: Version 2.0

• Balancing standardization with living document
  – Any substantive changes require changes in CRFs, databases, and risks confusion with future analysis

• Cohort A:
  – Clearer inclusion/exclusion criteria for M/XDR TB
  – Clarifying study visit timing/naming for longer treatment

• Cohort B:
  – Clarifications for TST and IGRA testing
  – Optional re-testing
Common Protocol: For discussion

- In development:
  - SOPs for process for RI members or RICC to recommend and decide on CP and/or Data Element Bank additions, deletions or changes

- Question: Develop modules for special studies, samples, TB populations or sites? Such as
  - TB meningitis
  - Diagnostic studies – all? Pediatric separate from adult?
  - EP TB
Common Protocol Data Elements

Bank

• Form the core of the platform for data harmonization across all RePORT Consortia.

• Come into play through the RePORT Case Report Forms
  – The backbone of each consortium's data repository, which eventually are intended to be pool-able, and merge-able across all RePORT Consortia in the context of specific research queries or projects.
Common Protocol Data Elements Bank

- The RICC serves as the keeper and curator of the data elements
- All data and databases are expected to conform to an English-language (i.e., CDISC-type format)
  - If CRFs are translated into local language for data collection, eventually must be back translated into English and verified as accurate (i.e., the same as the standard English RI CRFs).
  - Databases must use text fields where indicated, and these fields must be in the English language.
Common Protocol Data Elements
Bank

• Each consortium established data ctrs & coordinators
• RICC data manager, Lisa Saylor, having regular calls with consortium data centers
  – Working on having quarterly call with all, combined
• India and South Africa have sent dummy data
  – India data structure and elements good match with expectations/central data structure
  – South Africa data structure good match, language conforming, but dealing with missing data elements
    • Working on to identify what can be added, modified or will remain missing
Data Standardization: Despite Best Intentions...

- Two consortia collecting data in non-English language (Brazil, Portuguese & China, Mandarin)
- Problem anticipated:
  - Example, India and South Africa’s data include words ‘Yes’ and ‘No’, will not properly merge with data for the same question saying “Sim’ and ‘Não’, or Chinese characters.
  - Options: build an translation program; change to code
- Working with Brazil and China on finding solution
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## Snapshot of Specimens Collected Consortium-wide

<table>
<thead>
<tr>
<th>Country</th>
<th>PBMC</th>
<th>Whole Blood (DNA)</th>
<th>Urine</th>
<th>Plasma</th>
<th>Saliva</th>
<th>MTB Isolates</th>
<th>PAXGene</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>143</td>
<td>49</td>
<td>53</td>
<td>99</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brazil</td>
<td>4,735</td>
<td>4,050</td>
<td>19,116</td>
<td>19,399</td>
<td>2,835</td>
<td>1,572</td>
<td>1,861</td>
</tr>
<tr>
<td>South Africa</td>
<td>110</td>
<td>167</td>
<td>600</td>
<td>860</td>
<td>87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indonesia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>China</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>4,988</td>
<td>4,266</td>
<td>19,769</td>
<td>20,358</td>
<td>2,922</td>
<td>1,572</td>
<td>1,861</td>
</tr>
</tbody>
</table>
Biological specimens

- Specimens: tracking, future sharing, decision making discussions
RePORT TB-DM: Molecular Signatures of Tuberculosis-Diabetes Interaction [MSTDI]

- RePORT Brazil: Bruno Andrade (FIOCRUZ); Timothy Sterling (Vanderbilt).
- RePORT India: Padmapriya Darsini, (NIRT); Amita Gupta (JHMI); Hardy Kornfeld (UMMS); Vidya Mave (BJMC); Vijay Viswanathan (MV Diabetes Research Center).
- RePORT South Africa: Neil Martinson (PHRU); Jonathan Golub (JHMI);
- RePORT International Coordinating Center (RICC): Carol Hamilton (FHI 360)
Goal: generate preliminary data for each of the Aims to support a future PO1 proposal.

- **Aim 1.** To define the spectrum of dysglycemia in TB patients from South Africa, Brazil and India.
- **Aim 2.** To determine whether TB/DM comorbidity is associated with a qualitatively or quantitatively distinct baseline transcriptomic, proteomic, metabolomic and/or lipidomic profiles compared to TB and/or DM alone.
- **Aim 3.** To determine whether TB/DM comorbidity is associated with a qualitative or quantitative difference in the resolution of perturbed transcriptomic, proteomic, metabolomic and/or lipidomic profiles during and after antimicrobial chemotherapy.
RePORT Cross-consortium RFP

- Major goal: demonstrate cross-consortium data and specimen sharing
- Prospective profiling of eicosanoid and inflammatory balance in TB-diabetes
  - Bruno Andrade (Brazil), Alex Pym (South Africa) & Tim Sterling (Vanderbilt)
- Transcriptional signature of TB in advanced HIV
  - Valeria Rolla (Brazil), Dileep Kadam & Vidya Mave (India)
Conclusion, RePORT Future

- 4th Annual Meeting 2018 hopefully, pending US government’s budget decisions
- RePORT-sponsored scientific symposium scheduled for October 12th, Union Lung meeting in Guadalajara, Mexico, 2017